UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader
January 15, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

06-AUG-1998

MEMORANDUM

SUBJECT: ***FQPA SAFETY FACTOR RECOMMENDATIONS FOR THE ORGANOPHOSPHATES*** (A Combined Report of the Hazard Identification Assessment Review Committee and the FQPA Safety Factor Committee)

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)
and
Jess Rowland, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Margaret Stasikowski, Division Director
Health Effects Division (7509C)

Attached is a combined report of HED's Hazard Identification Assessment Review Committee (HIARC) and the FQPA Safety Factor Committee. This report includes the data presented in the July 7, 1998 Report of the HIARC, as well as the recommendations made by the FQPA Safety Factor Committee.

FQPA SAFETY FACTOR RECOMMENDATIONS FOR THE ORGANOPHOSPHATES

A Combined Report of the
Hazard Identification Assessment Review Committee and the
FQPA Safety Factor Committee

HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS
U.S. ENVIRONMENTAL PROTECTION AGENCY

August 6, 1998

Committee Members in Attendance

Members present were: William Burnam, Richard Kiegwin, Ray Kent, Deborah McCall, Kathy Monk, Daniel Rieder, Jess Rowland, Brenda Tarplee (Executive Secretary), Edward Zager (Chairperson)**.**

Hazard Identification Assessment Review Committee member present as observer: Susan Makris.

Report Preparation: _____

Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee

_____

Jess Rowland, Executive Secretary
Hazard Identification Assessment Review Committee

I. INTRODUCTION

The Hazard Identification Assessment Review Committee (HIARC) convened on May 12 - 14, 1998 for a comprehensive review of 40 Organophosphates which were originally reviewed by this Committee from September 1997 through May 1998.

The FQPA Safety Factor Committee (FQPA SFC) met on June 15 and 16, 1998 to evaluate hazard and exposure data for the organophosphates and to determine whether the data on each organophosphate are sufficiently reliable to permit reduction or removal of the 10-fold safety factor mandated by the Food Quality Protection Act of 1996 to protect infants and children from exposure to pesticides.

This report includes the results of both Committee meetings, including the recommendations for the FQPA safety factor (by the FQPA SFC) and a listing of additional uncertainty factors (by the HIARC) for use in the risk assessment process for the organophosphates.

II. HAZARD ASSESSMENT

HIARC's objective for this reassessment was to evaluate the following factors for consistency: 1) assessment of neurotoxicity studies for evidence of neuropathology; 2) quantitative and qualitative assessment of developmental and reproductive toxicity studies for enhanced susceptibility of infants and children as required by FQPA; 3) use of literature data in hazard identification; 4) identification of data gaps; 5) criteria used in triggering a developmental neurotoxicity study; 6) recommendations on FQPA Safety Factor to the FQPA Safety Committee; 7) the toxicological endpoints and doses for acute and chronic dietary as well as occupational and residential exposure risk assessments; 8) selection of dermal absorption factors for dermal risk assessments; and 9) application of FIFRA-related uncertainty factors.

Determination of susceptibility was performed for each pesticide on a case-by-case basis employing a weight-of-evidence assessment. The two primary concerns or factors that contributed to the decision-making process were: 1) enhanced **susceptibility** of the developing organism or offspring as might be observed in prenatal developmental toxicity studies in rodents and non-rodents, as well as multi-generation reproduction studies in rodents. The entire toxicity data base; particularly the hen and rat neurotoxicity studies, was evaluated for evidence of neuropathology (e.g., decreases in brain weights), which might be indicative of increased susceptibility of the developing nervous system; and 2) **uncertainty** related to the absence of complete toxicity data for the assessment of potential effects on infants and children.

The HIARC did not consider these two factors to be separate entities, but rather aspects of an information continuum that defined the uncertainties in how pesticides might affect humans. Thus in recommending an FQPA Safety Factor, an evaluation of susceptibility and uncertainty

issues might be altered by weight-of-evidence considerations such as: the severity of toxic effects in offspring in comparison to severity of maternal effects; a characterization of the dose-response curve for effects related to offspring; concordance of treatment-related effects between species and/or strains; knowledge of mode of action; and the level of confidence in the data base or critical studies.

The toxicology data base was evaluated for the neurotoxic, developmental and reproductive toxic potential of the 40 organophosphates. Of the 40, the data base was inadequate for Chlorpyrifos-methyl, Dicrotophos, and Temephos and no data were available for Fonofos, Isazophos, and Sulfotepp.

1. <u>Evaluation of Neurotoxicity</u>

The neurotoxicity data requirements include an acute delayed neurotoxicity study in hens, an acute neurotoxicity study in rats, and a subchronic neurotoxicity study in rats.

The acute delayed neurotoxicity study in hens was evaluated for organophosphate-induced delayed neurotoxicity (OPIDN); assessment of inhibition of acetylcholinesterase; and neurotoxic esterase (NTE); and histopathological assessment of brain, peripheral nerve, and spinal cord. Acute and the subchronic neurotoxicity studies in rats were usually evaluated for cholinesterase inhibition; neurobehavioral effects (Functional Observational Battery); and histopathology of the central and peripheral nervous system following single or repeated exposures.

All of the organophosphates are neurotoxic in that they may cause cholinesterase inhibition and related clinical signs, up to and including death following exposure. Organophosphates also may cause neuropathology of the visual system or effects on cognitive function, i.e., learning and memory as well as other effects on the nervous system. While acute and subchronic neurotoxicity studies may show some gross effects on the visual system or sensory function, these and other effects were not systematically evaluated at this meeting since the cause and effect relationship between cholinesterase inhibition and visual system effects has not been verified.

Of the 34 organophosphates that had neurotoxicity studies available, evidence of neuropathology was seen for the following:

CHEMICAL	EVIDENCE OF NEUROPATHOLOGY
Chlorpyrifos	Published studies have reported OPIDN in humans and animals (at lethal doses) and there have been case reports that indicate possible correlation of neurophysiological effects in humans.
Methamidophos	Positive neurotoxic esterase in a subchronic toxicity study in hens and delayed peripheral neuropathy in humans as well as polyneuropathy in hens at extremely high dose levels (greatly in excess of the hen LD_{50}) reported in published studies.
Methyl Parathion	Neuropathology in acute and subchronic neurotoxicity studies in rats and the chronic toxicity studies in rats.
Naled	In an acute delayed neurotoxicity study, axonal degeneration of the spinal cord was seen following a single oral dose. However, no neuropathy was seen after repeated dosing in the subchronic neurotoxicity study in hens. No evidence of neuropathology was seen following single or repeated dosing in rats.
ODM	Evidence of neuropathology was seen in hens following a single dose but no neuropathology was seen following repeated dose in hens. No evidence of neuropathology was seen following single or repeated dosing in rats.
Tribuphos	Evidence of OPIDN and neuropathology following repeated dermal applications in a subchronic delayed neurotoxicity study in hens.
Trichlorfon	Evidence of OPIDN and neuropathology in the acute delayed neurotoxicity study in hens and neuropathology in the subchronic neurotoxicity study in hens.

A study that evaluates the effects on the NTE is necessary for the following chemicals. The lack of NTE data in an otherwise acceptable negative hen study is not considered a major data gap, but indicates a need for confirmatory data (i.e., data to confirm that an effect on NTE does not occur).

ORGANOPHOSPHATES THAT REQUIRE ASSESSMENT OF NTE				
Azinphos-Methyl Ethion Methidathion Profenophos Trichlorfon	Cadusafos[1] Ethoprop Methyl Parathion Propetamphos	Coumaphos Fenitrothion Phorate Terbufos	Dimethoate Fenamiphos Phostebupirim Tetrachlorvinphos	Disulfuton[1] Isofenphos Pirimiphos-Methyl[1] Tribuphos

[1] Data gap exists for an acute delayed neurotoxicity study for these four chemicals.

2. Determination of Susceptibility

The HIARC evaluated the potential for enhanced susceptibility from exposure to these pesticides as required by the FQPA. This evaluation entailed the enhanced susceptibility of fetuses as compared to maternal animals following *in utero* exposure in rats and rabbits, as well as the enhanced susceptibility of pups as compared to adults in the two-generation toxicity study in rats. For most of these pesticides, following *in utero* exposures, developmental effects were observed at or above treatment levels which resulted in evidence of maternal toxicity. Following pre- and/or postnatal exposure in the two-generation reproduction toxicity study, in general, effects in the offspring were most often manifested as decreased pup viability at doses that caused considerable inhibition of cholinesterase activity and cholinergic signs in the parental animals. Since the effects seen in the offspring (e.g., decreased pup viability) are confounded by the presence of maternal toxicity, it is difficult to regard the offspring effects as indicative of developmental toxicity or enhanced susceptibility of young animals. In addition, in the prenatal developmental toxicity studies, the parameters evaluated are not comparable between the dams and the fetuses. While the dams are routinely evaluated for survival, clinical signs, body weight, body weight gain, food consumption, and certain reproductive parameters during the cesarian section, the fetuses undergo much more critical and more detailed evaluation. Therefore, the HIARC conducted a qualitative evaluation of the effects seen in the fetuses and/or pups as compared to the maternal/parental effects in order to ascertain whether the fetal/offspring effects were true indicators of susceptibility.

The primary effect for the organophosphates is the inhibition of cholinesterase activity. For most of the pesticides, however, comparative cholinesterase inhibition data for the dams and the pups were not available, thus precluding an evaluation of susceptibility based on this endpoint. When these data (i.e., comparative cholinesterase) were available however, no evidence of enhanced susceptibility was seen in the pups as compared to maternal animals (i.e., cholinesterase inhibition occurred at the same doses in the pups and parental animals).

i. Prenatal Developmental Toxicity Study in Rats

(a) The NOELs, LOELs, and endpoints selected for maternal and developmental toxicity in the prenatal developmental toxicity studies in rats are provided in **Attachment 1**. No evidence of enhanced susceptibility was observed for 33 of 40 organophosphates following *in utero* exposure to pregnant rats. For these chemicals, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals, nor was there evidence of an increase in severity of effects at or below maternally toxic doses. Of the remaining 7: an acceptable prenatal developmental toxicity study in rats was not available for Chlorpyrifos-methyl, Dicrotophos, Temephos, and Trichlorfon; and no data were available for Fonofos, Isazophos, and

Sulfotepp. It is noted that in pre/postnatal studies published in the open literature, evidence of enhanced susceptibility was demonstrated in rats for Chlorpyrifos following oral, subcutaneous and intraperitoneal administration and for Methyl Parathion via the subcutaneous, and intraperitoneal routes.

(b) For four chemicals (tabulated below), the NOELs and LOELs were the same for maternal and developmental toxicity (i.e., fetal effects were seen at the same dose that caused maternal toxicity) but the developmental (fetal) effects initially appeared to be more severe. Following a qualitative re-evaluation of the effects observed, the HIARC concluded that fetal effects occurred at dose levels causing similar or more severe maternal toxicity. The rationale for this conclusion is provided for each chemical.

DEVELOPMENTAL TOXICITY IN THE PRESENCE OF MATERNAL TOXICITY (DEVELOPMENTAL TOXICITY STUDIES-RATS)	
Cadusafos	Decreased fetal body weights occurred at levels causing cholinergic signs in the dams characterized as tremors, muscle fasciculations, exophthalmus and decreased activity.
Fenthion	Increased post-implantation losses were not accompanied by decreased litter sizes and no developmental effects were seen in the other parameters examined. Dams exhibited clinical signs and decreased body weights at the same dose that induced fetal effects. In addition, plasma, erythrocyte, and brain cholinesterase inhibition was seen in dams at doses lower than those causing fetal effects indicating that the dams were under stress.
Fenitrothion	There was an increased incidence of fetuses with skeletal variations at a dose that caused severe maternal toxicity, characterized as tremors and decreases in body weight and body weight gains.
Terbufos	The biological significance of the fetal effects (increases in early fetal resorptions and postimplantation losses) are questionable since similar effects (i.e., decreased litter size) were not seen in the two-generation study in rats. In addition, based on the results of other studies with this chemical, substantial cholinesterase inhibition may have occurred in dams (not measured in this study) and thus most likely contributed to the fetal effects.

ii. Prenatal Developmental Toxicity Study in Rabbits

(a) The NOELs, LOELs, and endpoints selected for the maternal and developmental toxicity in the prenatal developmental toxicity study in rabbits are provided in **Attachment 2.** No evidence of enhanced susceptibility was observed for 34 of 40 organophosphates following *in utero* exposure to pregnant rabbits. For these chemicals, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses. Of the remaining 6, an acceptable prenatal developmental toxicity study in rabbits was not available for Chlorpyrifos-methyl, Dicrotophos, and Temephos, and no data was available for Fonofos, Isazophos, and Sulfotepp.

(b) For five chemicals (tabulated below), the NOELs and LOELs were the same for maternal and developmental toxicity (i.e., fetal effects were seen at the same dose that caused maternal toxicity) but the developmental (fetal) effects appeared to be more severe. Following a qualitative evaluation of the effects observed, the HIARC concluded that fetal effects occurred at dose levels causing similar or more severe maternal toxicity. The rationale for this conclusion is provided for each chemical.

DEVELOPMENTAL TOXICITY IN THE PRESENCE OF MATERNAL TOXICITY (DEVELOPMENTAL TOXICITY STUDIES-RABBITS)	
Cadusafos	Severe maternal toxicity manifested as increased mortality and cholinergic signs at the same dose that caused an increase in total number of resorptions, decrease in total number of fetuses, and fetal death.
Ethyl Parathion	The dose that caused maternal deaths, increased moribundity, as well as decreases in body weight and body weight gains also caused a decrease in litter size.
Malathion	The slight increase in mean resorption sites was not accompanied by alteration in litter size and occurred at the same doses that caused decreased maternal body weights.
Phosmet	The dose that induced clinical signs and decreased body weight in dams, also resulted in skeletal variations observed in the fetuses.
Propetamphos	The increased resorptions were not accompanied by decreases in litter size.

iii. Two-Generation Reproduction Study in Rats

(a) The NOELs, LOELs, and endpoints selected for the parental systemic and offspring toxicity in the two-generation reproduction study is provided in **Attachment 3.** No evidence of enhanced susceptibility was observed for 35 of 40 organophosphates following pre and/or post natal exposure in the

two-generation reproduction study in rats (i.e., effects noted in offspring occurred at maternally toxic doses or higher). Of the remaining 5, an acceptable reproduction toxicity study in rats was not available for Chlorpyrifos-methyl, and Temephos, and no data were available for Fonofos, Isazophos, and Sulfotepp.

(b) For the following chemicals, the NOELs and LOELs were same for parental systemic toxicity and offspring toxicity (i.e., offspring effects were seen at the same dose that caused parental effects) but the offspring (pup) effects initially appeared to be more severe. Following a qualitative reevaluation of the effects observed, the HIARC concluded that the effects in the pups occurred at dose levels causing similar or more severe parental systemic toxicity. The rationale for this conclusion is provided for each chemical.

OFFSPRING TOXICITY IN THE PRESENCE OF PARENTAL TOXICITY (MULTIGENERATION REPRODUCTION TOXICITY STUDIES-RATS)	
Acephate	Decreased viability index and decreased pup body weight gain were seen at the same dose that caused parental toxicity characterized by clinical signs (alopecia and soft stools) and decreased body weight gain. Although the clinical signs in parental animals are not severe, comparison to other studies (subchronic) indicated that cholinesterase inhibition (not measured in this study) would have occurred in dams at the dose that caused offspring toxicity and thus most likely contributed to offspring toxicity. Also, the offspring effects were seen in the first generation only and not repeated in the second generation (i.e., not a consistent finding).
Dichlorvos	The abnormal estrous cycles observed in maternal animals most likely contributed to the offspring effects (reduced dams bearing litters, decreases in fertility and pregnancy indices) observed at the same dose.
Diazinon	Cholinesterase inhibition (ChEI) was not measure in parental animals in the reproduction study. ChEI was, however, was observed at lower doses in the other toxicity studies. Therefore it is postulated that ChEI occurred in the maternal animals at the same doses causing pup mortality and decreased pup weight gain observed during lactation at which time the pups were exposed to the chemical via the milk.
Fenitrothion	The dose that caused severe parental systemic toxicity (decreases in body weight and body weight gain as well as food consumption) was also associated with offspring toxicity (decreases in fertility index, number of implantation sites and viability) in one generation. However, similar offspring toxicity was not seen in the second generation (i.e., not replicated in the second generation).

OFFSPRING TOXICITY IN THE PRESENCE OF PARENTAL TOXICITY (MULTIGENERATION REPRODUCTION TOXICITY STUDIES-RATS)	
Isofenphos	Offspring toxicity manifested as increased pup mortality (reductions in lactation indices and mean litter size) and clinical signs (small to very small emaciated pups) were observed at the same dose that caused parental systemic toxicity (inhibition of plasma, erythrocyte and brain cholinesterase). The offspring toxicity was not considered to be more severe since: 1) the effects were observed only after postnatal Day 14 and not on other days (i.e., a single occurrence) and thus the biological significance is not known; 2) during that period (i.e., later portion of lactation), young rats consume approximately twice the diet per unit body weight as an adult rat consumes. Estimation of the test substance intake in pre-weaning animals is likely to be more than double the adult intake because of the availability of the test material both via the milk (lactation) and food, particularly after the mid point of lactation; and 3) the dose that caused the offspring toxicity also caused cholinesterase inhibition (all three compartments) in parental animals.
Malathion	The decreases in the F1a and F2b pup body weight occurred at a lower dose than the dose that caused parental toxicity; this was not a true indication of enhanced susceptibility because: 1) pup body weight decrements were primarily observed at postnatal Day 21; 2) during that period, young rats consume approximately twice the diet per unit body weight as an adult rat consumes; and 3) the estimation of the test substance intake in pre-weaning animals is likely to be more than double the adult intake because of the availability of the test material both via the milk (lactation) and food, particularly after the mid point of lactation.
Methamidophos	Substantial cholinesterase inhibition was seen at lower doses in other toxicity studies conducted with rats indicating that cholinesterase inhibition most likely occurred in parental animals at a dose that caused offspring toxicity (decreased pup viability). Also this effect was seen only on postnatal Day 14 and only in one generation. It is noted that decreased pup viability was also seen with Acephate, a related organophosphate, at the same dose that caused parental toxicity.
Oxydemeton-methyl (ODM)	The same dose that caused cholinesterase inhibition in parental animals also caused offspring toxicity (decreased viability index, decreased litter size at birth, and decreased pup body weight gain during lactation). In addition, no enhanced susceptibility was seen in adults vs. fetuses based on comparative cholinesterase inhibition data (i.e., cholinesterase inhibition occurred at the same doses in the pups and the parental animals).

OFFSPRING TOXICITY IN THE PRESENCE OF PARENTAL TOXICITY (MULTIGENERATION REPRODUCTION TOXICITY STUDIES-RATS)	
Phorate	The same dose that caused severe parental toxicity (tremors and inhibition of plasma and brain cholinesterase activity) also caused decreased pup survival and pup body weight.

3. Summary of the Hazard Assessments

The HIARC's assessments for neurotoxicity, enhanced susceptibility, the need for additional data, or the requirement of a developmental neurotoxicity study is summarized in **Attachment 4**.

III. EXPOSURE ASSESSMENT

1. Dietary Exposure

i. Considerations

Dietary exposure assessment addresses the potential for exposure to infants and children from pesticide residues in food. Considerations include: the evaluation of use patterns; actual dietary consumption and exposure data or estimates; and the completeness of the data, including characterization of uncertainties pertaining to dietary exposure.

For each pesticide, the following information was evaluated (as available):

- Whether the pesticide has major agricultural uses.
- Range of application rates and frequency of applications.
- Range of established tolerances and the nature of the metabolites requiring regulation.
- Whether the pesticide is used on commodities preferentially consumed by infants and children (such as citrus fruit, pome fruit, cereal grains, milk, soybeans, etc.); and if so, which ones.
- Whether the pesticide is "systemic", indicating residues are distributed throughout the commodity and not likely to be removed by preparation such as washing or peeling.
- Available residue data sources for the pesticide (field studies, FDA monitoring data, PDP monitoring data, etc.).
- Brief description of the range and frequency of positive residue findings for the pesticide.
- Extent of possible refinement to the Dietary Risk Evaluation System (DRES) analyses (ie., tolerance levels, anticipated residues (ARs), percent crop treated (%CT), monitoring data, Monte Carlo distributional analysis, etc.).

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ii. Summary of Dietary Exposure Assessments

A summary table of the considerations used in the dietary exposure assessments for each of the OPs is presented in **Attachment 5**. This information was obtained from the HED Reregistration Eligibility Document (RED) Chapters or executive summaries of the HED RED Chapter, Dietary Risk Evaluation System (DRES) analyses reports, and/or risk characterization summaries.

2. Drinking Water Exposure

i. Considerations

Drinking water exposure assessment addresses the potential for exposure to infants and children from contaminated water sources. Considerations include: actual exposure data or estimates; the completeness of the environmental fate data, including characterization of uncertainties, as well as the evaluation of the use patterns pertaining to drinking water exposure.

For each pesticide, the following information was evaluated (as available):

- Completeness of the environmental fate data base.
- Whether the compound or its degradate(s) has the potential to leach to drinking water sources.
- Whether ground and/or surface water studies (or other appropriate, reliable, targeted monitoring data) were used to calculate estimated environmental concentrations (EECs) for the pesticide; and if so, whether the studies were conducted in vulnerable areas at maximum label rates.
- Whether ground water and surface water EECs were based on modeling; and if so, the model and tier used.
- Description of the extent of exposure and the potential population affected.

ii. Summary of Drinking Water Exposure Assessments

A summary table of the considerations used in the drinking water exposure assessments for each of the OPs is presented in **Attachment 6**. This information was obtained from the HED Reregistration Eligibility Document (RED) Chapters or executive summaries of the HED RED Chapter, EFED Drinking Water Assessment reports, and/or risk characterization summaries.

3. Residential Exposure

i. Considerations

Residential exposure assessment addresses the potential for exposure to infants and children from non-dietary, non-occupational sources. Considerations include: the evaluation of use patterns; actual exposure data or estimates; and the completeness of the data, including characterization of uncertainties pertaining to residential exposure.

For each pesticide, the following information was evaluated (as available):

- Whether infants and children could be exposed from the use of the pesticide.
- Whether pesticide-specific or site-specific data are available for the exposure assessment.
- Whether Pesticide Handler Exposure Data base (PHED) data is used; and if so, whether the scenarios used reflect the actual use pattern.
- Whether the *Draft Standard Operating Procedures for Residential Exposure Assessments* were used as the basis for post-application exposure calculations; and if so, a description of any deviations from SOP calculations.
- Whether other models were used; and if so, the model and tier used.
- Whether any biological exposure or epidemiology data are available (e.g., incident reports, CDC monitoring data, etc.); and if so, a description of the data.
- Whether 100% dermal absorption is assumed in the exposure assessment when dermal endpoints are derived from oral studies.

ii. <u>Summary of Residential Exposure Assessments</u>

A summary table of the considerations used in the residential exposure assessments for each of the OPs is presented in **Attachment 7.** This information was obtained from the HED Reregistration Eligibility Document (RED) Chapters or executive summaries of the HED RED Chapter, and/or risk characterization summaries.

IV. FQPA SAFETY FACTOR RECOMMENDATION AND RATIONALE

In determining whether to recommend removal, reduction, or retention of the FQPA safety factor for each of the organophosphates, the Committee considered: 1) the hazard and dose response evaluations; 2) the exposure assessment(s); and 3) the characterization of both the hazard and exposure data base.

1. Recommendations for the FQPA Safety Factor

The FQPA Safety Factors recommended by the FQPA Safety Factor Committee are presented below:

Removed (1x)	Reduced to 3x	Retained (10x)
Acephate Azinphos-methyl Bensulide Chlorethoxyfos Diazinon Dimethoate Ethion Ethoprop Ethyl Parathion Fenamiphos Fenitrothion Fenthion Malathion Methidathion Naled Profenofos Propetamphos Tetrachlorvinphos	Coumaphos Dichlorvos (DDVP) Disulfoton Isofenphos Methamidophos Phorate Phosmet Phostebupirim Pirimiphos-methyl Terbufos	Cadusafos Chlorpyrifos Methyl parathion Oxydemeton-methyl Tribuphos (DEF) Trichlorfon

Retained (10x) - Inadequate Tox Data base	Other
Chlorpyrifos-methyl Dicrotophos Temephos	Fonofos: cancellation proceedings are in place. Isazophos-methyl: no toxicology or exposure data are available for an adequate assessment. Sulfotepp: FQPA not applicable (greenhouse use only).

2. Rationale for the Recommendations for the FQPA Safety Factor

i. FQPA Safety Factor Removed (1x)

For **Acephate, Azinphos-methyl, Bensulide, Chlorethoxyfos, Diazinon, Dimethoate, Ethion, Ethoprop, Ethyl Parathion, Fenamiphos, Fenthion, Fenitrothion, Malathion, Methidathion, Naled, Profenofos, Propetamphos, and Tetrachlorvinphos** the FQPA safety factor is **removed** based on the following factors:

(a) In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.

(b) In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pup when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher).

(c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies.

(d) There is no concern for positive neurological effects from the available neurotoxicity studies or for histopathology in the central nervous system from the other toxicological studies (e.g., subchronic rat, chronic dog, chronic mouse and rat).

(e) The toxicology data base is complete and there are no data gaps according to the Subdivision F Guideline requirements.

(f) Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary and residential exposure and to provide a screening level drinking water exposure assessment.

ii. FQPA Safety Factor Reduced (3x)

For **Coumaphos, Dichlorvos, Disulfoton, Isofenphos, Methamidophos, Phorate, Phosmet, Phostebupirim, Pirimiphos-methyl, and Terbufos** the FQPA safety factor is **reduced to 3x.**

In general, the hazard (based on the neurotoxicity, developmental and reproductive toxicity studies) and exposure (dietary, drinking water and residential) assessments for these ten pesticides indicate the following:

(a) In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.

(b) In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pups when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher).

(c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies.

(d) There is no concern for positive neurological effects from the available neurotoxicity studies or for histopathology in the central nervous system from the other toxicological studies (e.g., subchronic rat, chronic dog, chronic mouse and rat studies).

(e) Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary and residential exposure and to provide a screening level drinking water exposure assessment.

However, there were partial data gaps for the neurotoxicity studies (7 pesticides) and evidence of neuropathology (2 pesticides) which led to either requiring or reserving the requirement for a developmental neurotoxicity study for these pesticides (9 total). When a developmental neurotoxicity study is required, it is because this study will provide additional data (e.g., potential increased susceptibility, effects on the development of the fetal nervous system, etc.). When the requirement for a developmental neurotoxicity study is placed in reserve status, the Agency will make the final requirement decision following evaluation of the results of the neurotoxicity studies (i.e., data gaps). For one pesticide there was concern for decreased brain weights in guinea pig fetuses as reported in the open literature, as well as uncertainty in the chemical specific residential exposure data.

Therefore, the Committee determined that a FQPA safety factor was necessary for these pesticides. However, it was determined that the 10x factor can be reduced to 3 x and the rationale is provided below:

> Specifically, for **Coumaphos, Disulfoton, Phorate, Phosmet, Phostebupirim, Pirimiphos-methyl, and Terbufos** the FQPA safety factor is **reduced to 3x** because of data gaps for one of the neurotoxicity studies (i.e., acute delayed neurotoxicity-hen and/or acute or subchronic-rat) and the requirement for a developmental neurotoxicity study placed in reserve status. The results of these neurotoxicity studies may "trigger" the requirement of a developmental neurotoxicity study which in turn will provide additional data (e.g., potential increased susceptibility, effects on the development of the fetal nervous system, etc.).

For **Methamidophos** and **Isofenphos** there was evidence of neuropathology reported in the open literature indicating that an FQPA safety factor is appropriate. The Committee, however, determined that the 10x factor can be **reduced** to **3x** because: 1) there was no increased susceptibility seen in studies submitted to the Agency, 2) there was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies, 3) there were no positive neurological effects in other toxicology studies; 4) the toxicology data base is complete; and 5) no concern is indicated by exposure assessment.

> Specifically for **Methamidophos,** polyneuropathy was observed in hens at high doses, as well as the occurrence of delayed peripheral neuropathy in humans (through accidental occupational poisoning, suicide attempts, or ingestion of contaminated vegetables) as reported in the open literature.
>
> Specifically for **Isofenphos,** delayed neuropathy was observed in an agricultural worker exposed to multiple pesticides including Isofenphos (as reported in the open literature), as well as concern for a number of poisoning incidents involving children (ages $\leq$ 5) reported by the Poison Control Center (1985-92 data).

For both pesticides, these concerns "triggered" the requirement for a developmental neurotoxicity study which in turn will provide additional data (e.g., potential increased susceptibility, effects on the development of the fetal nervous system, etc.). For Isofenphos, the developmental neurotoxicity study was requested by the FQPA Safety Factor Committee.

Specifically for **Dichlorvos (DDVP),** decreased brain weights in guinea pig fetuses was reported in the open literature. Additionally, there is concern for uncertainty in the chemical specific residential exposure data which warrants the FQPA safety factor. The Committee, however, determined that the 10x factor can be **reduced to 3x** because: 1) there was no increased susceptibility seen in studies submitted to the Agency, 2) there was no evidence of abnormalities in the development of the fetal nervous system in pre/postnatal studies or concern for positive neurological effects in other toxicology studies; and 3) the toxicology data base is complete.

In addition, the HIARC determined that a prenatal developmental toxicity study in guinea pigs is necessary to confirm the findings of the literature study; and therefore, the requirement of developmental neurotoxicity study is placed in reserve status pending the results of the aforementioned study.

iii. <u>FQPA Safety Factor Retained (10x)</u>

For **Cadusafos, Chlorpyrifos, Methyl Parathion, Oxydemeton-methyl, Tribuphos and Trichlorfon**, the FQPA safety factor of **10x** is **retained.**

The reasons for retaining the FQPA safety factor (10x) are based on: data gaps for <u>all three</u> neurotoxicity studies (1 pesticide); evidence of increased susceptibility (2 pesticides); concern for heritable effects (1 pesticide); evidence of neuropathology, as well as data gaps for neurotoxicity studies (1 pesticide); and evidence of

neuropathology, data gaps for neurotoxicity and prenatal developmental toxicity studies (1 pesticide).

In general, hazard (based on the neurotoxicity, developmental, and reproductive toxicity studies) and exposure (dietary, drinking water, and residential) assessments indicate:

(a) In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.

(b) In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pup when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher).

(c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies submitted to the Agency.

(d) Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary and residential exposure and to provide a screening level drinking water exposure assessment.

Specifically for **Cadusafos,** there are data gaps for all three neurotoxicity studies (i.e., acute delayed in hens as well as acute and subchronic studies in rats) which places the requirement of a developmental neurotoxicity study in reserve status.

Specifically for **Chlorpyrifos** and **Methyl parathion,** in studies conducted at various scientific laboratories and reported in the open literature, neuropathology was observed in animals and/or humans, and evidence of increased susceptibility was seen in prenatal developmental toxicity studies in rats following oral, subcutaneous and/or intraperitoneal administrations. Although the subcutaneous and intraperitoneal routes of exposure are not traditional (i.e., oral), the Committee determined that the demonstration of increased susceptibility, as well as occurrence of neuropathology warrants the 10x safety factor. Also, these concerns result in the requirement of a developmental neurotoxicity study for both of these pesticides. *Note: The Agency acknowledges the recent receipt of a developmental neurotoxicity study for Chlorpyrifos which is currently under review.*

Specifically for **Oxydemeton methyl** there is concern for heritable effects as demonstrated in an *in vivo* mouse spot test. This test was positive for the induction of somatic cell mutations following intrauterine exposure of embryos. This adverse effect is clearly associated with the developing embryos thus warranting the 10x safety factor. A reproducible, concentration-dependent increase in mutation was seen at doses lower than the level causing maternal toxicity. In addition, there was valid evidence of DNA strand breaks in rat testes cells in an *in vitro* alkaline elution assay (not confirmed *in vivo*). Based on these

concerns, the HIARC required a mouse specific locus test (this requirement was "triggered"by the positive mouse spot test).

Specifically for **Tribuphos,** OPIDN and neuropathology was observed following repeated dermal applications in hens, ocular effects and neuropathology were also seen in several species. In addition, there are data gaps for all three neurotoxicity studies. The concern for the effects seen after dermal exposure, in conjunction with the data gaps resulted in the requirement of a developmental neurotoxicity study.

Specifically for **Trichlorfon,** the safety factor is retained based on a number of factors including occurrence of neuropathology, as well as the presence of data gaps. Neurotoxicity concerns include the presence of OPIDN and neuropathology in hens, as well as decrease in brain weights in guinea pig fetuses in a prenatal developmental toxicity study identified in open literature. Data gaps include acute and subchronic neurotoxicity studies in rats and a prenatal developmental toxicity study in rats. These factors resulted in the requirement of a prenatal developmental toxicity study in guinea pigs (to verify the findings reported in the open literature). The developmental neurotoxicity study in rats is placed in reserve status pending the results of the developmental toxicity study in the guinea pigs.

For **Chlorpyrifos-methyl, Dicrotophos, and Temephos** the FQPA safety factor is **retained** solely because of the inadequacy of the toxicology data base which precluded an evaluation of potential enhanced susceptibility to infants and children.

iv. FQPA Safety Factor Not Determined

An FQPA safety factor could not be determined for: **Fonofos**, since cancellation proceedings are in place for this pesticide; and **Isazophos-methyl**, for which there are no toxicology or exposure data available.

v. FQPA Safety Factor Not Applicable

An FQPA safety factor is not applicable to **Sulfotepp** since the only registered use is for greenhouses and there is no potential for exposure via the dietary, drinking water, or residential routes.

3. Application of the FQPA Safety Factor

For most of the organophosphates, the FQPA safety factor recommendations result from datagaps in the toxicology data requirements. The lack of a complete database encompasses the general population and is not limited to any one subpopulation.

For those organophosphates that require a developmental neurotoxicity study, the results from this study may be used in selecting endpoints that are applicable to risk assessments for all population groups.

When a developmental neurotoxicity study is required, it is generally recognized that the developmental effects seen in this study are considered to be "acute" effects and thus relevant for acute dietary risk assessment since it is presumed that developmental effects

may arise from a single exposure. However, the results from this study may also be applicable for chronic dietary risk assessments because: 1) an extended dosing regimen (day 6 of gestation to day 10 postnatal) is used in the study; 2) developmental effects can occur at doses lower than those that induce chronic effects; and 3) adverse effects on human development can occur from birth through adolescence (long term process). Thus, the uncertainty related to the absence of a developmental neurotoxicity study makes it appropriate to apply a FQPA safety factor for acute and chronic dietary and non-dietary risk assessments for the general population including infants and children.

The FQPA safety factors are relevant for acute and chronic dietary risk assessments since the endpoints are based on plasma, red blood cell, and/or brain cholinesterase inhibition seen following single (acute) and/or repeated (chronic) exposures. Furthermore, it is also applied when performing residential (dermal and inhalation) exposure risk assessments, which utilize the oral endpoints with appropriate absorption factors for route-to-route extrapolation.

V. COMBINED UNCERTAINTY FACTORS FOR RISK ASSESSMENT

In risk assessment calculations, the FQPA safety factor recommendations must be considered along with the conventional Uncertainty Factors (i.e., 10x for interspecies extrapolation and 10x for intraspecies variability), and any additional Uncertainty Factors (UFs) assigned by the HIARC for various toxicological considerations. Examples of such considerations include the use of a LOEL when a NOEL was not established in the critical study or the use of a single sex human study. Presented below are the conventional Uncertainty Factors, the additional Uncertainty Factors assigned as needed by HIARC, the FQPA safety factor, and the resulting combined factors.

PESTICIDE	EXPOSURE SCENARIO	CONVEN-TIONAL FACTOR	ADDITIONAL UNCERTAINTY FACTOR (REASONS)	FQPA FACTOR	COMBINED FACTOR
Acephate	All[1]	100	No additional factor required	1	100
Azinphos-methyl	Acute Chronic No residential uses	100 100	3 (use of LOEL) No additional factor required	 1	300 100
Bensulide	All	100	No additional factor required	1	100
Cadusafos	Acute Chronic No residential uses	100	No additional factor required	10	1000

[1] "All" indicates acute dietary, chronic dietary, and residential exposure scenarios.

PESTICIDE	EXPOSURE SCENARIO	CONVEN-TIONAL FACTOR	ADDITIONAL UNCERTAINTY FACTOR (REASONS)	FQPA FACTOR	COMBINED FACTOR
Chlor-ethoxyfos	Acute Chronic No residential uses	100	No additional factor required	1	100
Chlorpyrifos	All	10	No additional factor required	10	100
Coumaphos	Acute Chronic No residential uses	100	No additional factor required	3	300
Diazinon	Acute Chronic Residential, Dermal[2] Residential, Inhalation[3]	100 10 10 100	No additional factor required 3 (NOEL/LOEL and one sex) [4] 3 (NOEL/LOEL and one sex) 3 (use of a LOEL)	1	100 30 30 300
Dimethoate	All	100	No additional factor required	1	100
Disulfoton	All	100	No additional factor required	3	300
DDVP	Acute Chronic Residential: Short-Term, dermal Intermediate, dermal Long-Term, dermal Inhalation	10 100 10 10 NA 100	No additional factor required No additional factor required No additional factor required 3 (use of a LOEL) Not required/No use No additional factor required	3	30 300 30 100 NA 300

[2] For all time periods (Short-, Intermediate-, and Long-Term) unless otherwise stated.

[3] For all time periods (Short-, Intermediate-, and Long-Term) unless otherwise stated.

[4] Diazinon: closeness of NOEL/LOEL established in the study.

PESTICIDE	EXPOSURE SCENARIO	CONVEN -TIONAL FACTOR	ADDITIONAL UNCERTAINTY FACTOR (REASONS)	FQPA FACTOR	COMBINED FACTOR
Ethion	Acute	10	No additional factor required		10
	Chronic	10	10 (use of a LOEL and other	1	100
	No residential uses		reasons)[5]		
Ethoprop	Acute	100	No additional factor required	1	100
	Chronic				
	No residential uses				
Ethyl	Acute	100	No additional factor required		100
parathion	Chronic	100	3 (use of a LOEL)	1	300
	No residential uses				
Fenamiphos	Acute	100	3 (use of a LOEL)		300
	Chronic	100	No additional factor required	1	100
	No residential uses				
Fenitrothion	All	100	No additional factor required	1	100
Fenthion	Acute	10	No additional factor required		10
	Chronic	10	3(threshold NOEL/LOEL)	1	30
	No residential uses				
Isofenphos	Acute	100	3 (use of a LOEL)		1000
	Chronic	100	No additional factor required		300
	Residential, Dermal and			3	
	Inhalation: Short-Term	100	3 (use of a LOEL)		1000
	Intermediate and Long-				
	Term	100	No additional factor required		300
Malathion	Acute	100	No additional factor required		100
	Chronic	100	No additional factor required		100
	Residential:			1	
	Dermal (all time periods)	100	No additional factor required		100
	Inhalation, Short-Term	100	No additional factor required		100
	Intermediate and				
	Long-Term	100	3 (use of a LOEL)		300

[5] A UF of 10 was necessary due to the lack of a NOEL in the critical (human) study and the possibility that brain cholinesterase could be inhibited at dose levels comparable to those causing plasma cholinesterase inhibition as demonstrated in animal studies.

PESTICIDE	EXPOSURE SCENARIO	CONVEN-TIONAL FACTOR	ADDITIONAL UNCERTAINTY FACTOR (REASONS)	FQPA FACTOR	COMBINED FACTOR
Metho-midophos	Acute Chronic No residential uses	100	No additional factor required	3	300
Methidathion	Acute Chronic No residential uses	100	No additional factor required	1	100
Methyl parathion	Acute Chronic No residential uses	100	No additional factor required	10	1000
Naled	All	100	No additional factor required	1	100
Oxydemeton-methyl	Acute Chronic No residential uses	100 10	3 (use of a LOEL) No additional factor required	10	3000 100
Phorate	Acute Chronic No residential uses	100	No additional factor required	3	300
Phosmet	All	100	No additional factor required	3	300
Phostebupirim	Acute Chronic No residential uses	100	No additional factor required	3	300
Pirimiphos-methyl	Acute Chronic No residential uses	10 10	No additional factor required 30 (use of a LOEL + data gaps) [6]	3	30 1000
Profenofos	Acute Chronic No residential uses	100	No additional factor required	1	100
Propetamphos	All	100	No additional factor required	1	100
Terbufos	Acute Chronic No residential uses	100	No additional factor required	3	300
Tetra-chlorvinphos	All	100	No additional factor required	1	100

[6] Pirimiphos-methyl: Data gaps exists for a chronic toxicity study in dogs and a chronic/carcinogenicity study in rats.

PESTICIDE	EXPOSURE SCENARIO	CONVEN -TIONAL FACTOR	ADDITIONAL UNCERTAINTY FACTOR (REASONS)	FQPA FACTOR	COMBINED FACTOR
Tribuphos	Acute	100	No additional factor required	10	1000
	Chronic	100	No additional factor required		1000
	No residential uses				
Trichlorfon	Acute	10	No additional factor required		100
	Chronic	100	No additional factor required	10	1000
	Residential	100	No additional factor required		1000

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Name	Division/Branch
Edward Tagl	HED/RAB I
Daniel Rieder	EFED
Susan Makris (observer)	HED/TOX I
Kirk Kerrigan / Dennis McCall	RD
Ray Kent	HED/C&B 2
W. Dykstra	HED/SAB
Jess Rowland	HED/SAB
Kathy Monk	SRRD
Brenda Tarplee	HED/RAB 1

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